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*Division of Biostatistics (HFM-215)*

# Statistical Review

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**SUBJECT:** *sBLA for BOTOX for the use in the treatment of glabellar lines*

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## BACKGROUND

The purpose of this BLA submission is to add a new indication to the label for the use of BOTOX in the treatment of glabellar lines. The clinical program to support the use of BOTOX for the treatment of glabellar line comprised two multi-center, double-blind, randomized, placebo controlled trials (Protocols 010 and 023) and an open-label study (Protocol 018) that included only those subjects who had completed one of the controlled studies and qualified for re-injection.

Use of BOTOX for the treatment of strabismus, blepharospasm associated with dystonia, and cervical dystonia has been approved in U.S.A. In some countries, BOTOX has additional indications, including approvals for glabellar lines.

## PROTOCOL 010

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison of BOTOX and placebo in the treatment of glabellar lines. Subjects whose glabellar lines were at least moderate severity at maximum frown were eligible for the study. It was planned that 256 subjects would be enrolled and randomly assigned in a ratio of 3:1 to receive a single treatment of intramuscular injections at five sites of either BOTOX (20 units) or placebo. Treatment group assignment was stratified by age group (≤50 years and > 50 years). Post injection evaluations were scheduled on days 7, 30 (key timepoint), 60, 90, and 120.

A total of 264 subjects were enrolled in the study, with 203 subjects randomized to BOTOX and 61 randomized to placebo. All but three subjects, two in the BOTOX group and one in the placebo group, completed the study. Subject ——— (BOTOX arm) moved to another state after the day 90 visit, subject ——— (BOTOX arm) discontinued 28 days after study treatment because she had to take care for ill husband and was unable to come to scheduled appointment. Subject ——— was randomized to the placebo arm but not treated (voluntarily withdrew because of the need to remain in the office for 30 minutes after the study injection). There are nine subjects with major protocol violations: Six subjects (five in the BOTOX and one in the placebo group) had concomitant facial procedures during the study and three subjects were not evaluated by different investigators at days 7 and 30.

The analysis for efficacy was intent-to-treat (ITT), including all randomized subjects. The two co-primary efficacy endpoints were the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines at day 30. The secondary efficacy variable in this study is investigator's assessment of glabellar line severity at rest. The primary procedure of handling missing data for the three efficacy variables are the mean imputation, i.e., at each visit, the mean of all non-missing data across both treatment groups was rounded to an integer value and used to replace these missing values. If a subject discontinued prior to day 30 visit, missing values were replaced up to and including the day 30 visit. All tests were two-sided. BOTOX was claimed more efficacious than placebo only when both co-primary endpoints were statistically significant at the significance level of 0.05 in favor of BOTOX at day 30.

### 1.0 Investigator's Assessment of Glabellar Line Severity at Maximum Frown

One of the two primary endpoints is investigator's assessment of glabellar line severity at maximum frown at day 30. A photoguide, which gave photographic examples of each glabellar line severity, was provided to each study center to assist in grading the severity of glabellar lines. Glabellar line severity scores were coded as 0=none, 1=mild, 2=moderate, and 3=severe.

In the primary analysis, the scores were dichotomized to represent responders (score≤1) and non-responders (score≥2). A Mantel-Haenszel (MH) test stratified by age group (≤50 vs. > 50) was performed to compare the proportions of responders between the two treatment groups. The results are shown in Table 1. The proportion of responders in the BOTOX group was statistically significantly higher than that in the placebo group. At day 30, which was defined as the key timepoint, there was approximately an 82-percentage-point difference in response rates favoring the BOTOX group over the placebo group, exceeding the 30-percentage-point difference required by the first part of the protocol definition of clinically significant results.

**Table 1. Responder Rate for Investigator's Assessment of Glabellar Line Severity at Maximum Frown (% and number of subjects with severity of none or mild)**

| Visit | BOTOX | Placebo | Difference (95% C.I.) | P-value |
|---|---|---|---|---|
| Day 7 | 82.3% (167/203) | 4.9% (3/61) | 77.4 (69.8, 84.9) | < 0.001 |
| Day 30 | 83.7% (170/203) | 1.6% (1/61) | 82.1 (76.1, 88.1) | < 0.001 |
| Day 60 | 74.8% (151/202) | 0.0% (0/60) | 74.8 (68.8, 80.7) | < 0.001 |
| Day 90 | 50.5% (101/202) | 0.0% (0/60) | 50.0 (43.1, 56.9) | < 0.001 |
| Day 120 | 26.2% (53/202) | 0.0% (0/60) | 26.2 (20.2, 32.2) | < 0.001 |

In addition to the primary analysis, the sponsor also conducted a variety of different sensitivity analyses and analyses on subgroup population. The mean baseline (day 0) severity at maximum frown as rated by the investigator was 2.6 in both treatment groups, but the mean rating in the BOTOX group decreased from 1.75 at day 30 to 0.71 at day 120. These decreases were statistically significantly greater than those in the placebo group ($p<0.001$) when the raw severity scores were analyzed using the exact Smirnov test. When the nine subjects who had major protocol violations were excluded from the analysis, the results did not differ from those presented for the overall population.

Subgroup analyses of this endpoint by age group, sex, race, investigator, baseline score, and whether subjects had prior BOTOX treatment for facial lines at study entry gave results generally similar to those for the overall population. However, response rates with BOTOX tended to be higher for subjects ≤50, for female, for Caucasians, for subjects who had prior BOTOX treatment, and for subjects whose baseline severity score was moderate.

## 2.0. Subject's Global Assessment of Change in Appearance of Glabellar Line Severity

The other primary efficacy endpoint is subject's global assessment of change in appearance of glabellar line severity at day 30. For this measurement, subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your injection?" The responses were graded a 9-point scale in which +4 =complete improvement, 0 = unchanged, and –4 = very marked worsening.

In the primary analysis, subject's global assessment also was dichotomized to represent responders (scores≥2) and non-responders (scores≤1). A Mantel-Haenszel (MH) test stratified by age group was performed to evaluate the equality of the proportions of responders between the two treatment groups. The results are shown in Table 2. The proportion of subjects reporting moderate or better improvement (score≥2) in the appearance of glabellar lines in the BOTOX group was statistically significantly higher than that in the placebo group. At day 30, which was defined as the key timepoint, there was approximately an 89-percentage-point difference in response rates favoring the BOTOX group over the placebo group, exceeding the 25-percentage-point difference required by the first part of the protocol definition of clinically significant results.

**Table 2. Responder Rate for Subject's Assessment of Change in Appearance of Glabellar Lines (% and number of subjects with at least moderate improvement)**

| Visit | BOTOX | Placebo | Difference (95% C.I.) | P-value |
|---|---|---|---|---|
| Day 7 | 85.7% (174/203) | 4.9% (3/61) | 80.8 (73.5, 88.1) | < 0.001 |
| Day 30 | 91.1% (183/203) | 1.6% (1/61) | 88.5 (83.3, 93.7) | < 0.001 |
| Day 60 | 84.7% (171/202) | 1.7% (1/60) | 83.0 (77.1, 88.9) | < 0.001 |
| Day 90 | 65.8% (133/202) | 1.7% (1/60) | 64.2 (56.9, 71.5) | < 0.001 |
| Day 120 | 41.1% (89/202) | 0.0% (0/60) | 44.1 (37.2, 50.9) | < 0.001 |

In addition to the primary analysis, the sponsor also conducted a variety of different sensitivity analyses and analyses on subgroup population. By day 7 and day 60, the mean rating in the BOTOX group reflected an improvement of more than 2.5 grades, reaching 3 grades at day 30. This improvement dropped to 2 grades at day 90 and 1.4 grades at day 120. These results were statistically significantly ($p<0.001$) better at every visit than those in the placebo group which never exceeded 0.23 grades. When the nine subjects who had major protocol violations were excluded from the analysis, the results did not differ from those presented for the overall population.

Subgroup analyses of this endpoint by age group, sex, race, investigator, baseline score, and whether subjects had prior BOTOX treatment for facial lines at study entry gave results generally similar to those for the overall population. However, response rates with BOTOX tended to be higher for subjects ≤50, for female, for Caucasians, for subjects who had prior BOTOX treatment, and for subjects whose baseline severity score was moderate.

## 3.0 Investigator's Assessment of Glabellar Line Severity at Rest

Investigator's assessment of glabellar line severity at rest among the potential responders is the secondary efficacy variable in this study. Potential responders were those subjects who had a baseline glabellar line severity score of moderate or severe at rest. This subgroup comprised 68 subjects in BOTOX group and 17 subjects in the placebo group. The proportion of these subjects whose glabellar line severity was rated as none or mild at rest was significantly higher in the BOTOX group than in the placebo group at every follow-up visit (p-values range from 0.022 to < 0.001). The response rates in the BOTOX group were 69%, 79%, 77%, 78%, and 68% on days 7, 30, 60, 90, and 120, respectively, compared to 29%, 24%, 29%, 41%, and 35% in the placebo group.

Analyzed across all subjects, the proportion of subjects whose glabellar line severity was rated as none or mild at rest was also significantly higher in the BOTOX group than in the placebo group at every follow-up visit. The response rates in the BOTOX group were 93% and 88% on days 30 and 120, respectively, compared to 75% and 77% in the placebo group.

## 4.0 Safety

Adverse events were reported for 47% of subjects treated with BOTOX and 37% subjects treated with placebo. The most frequently reported adverse event was headache, which was reported for 15% of subjects treated with BOTOX or placebo. No subjects discontinued the study due to adverse events. There were 2 serious adverse events, thrombophlebitis and ovarian disorder. Both events occurred in subjects treated with BOTOX and were considered unrelated to study medication. The only adverse event reported notably more frequently for subjects treated with BOTOX than for subjects treated with placebo was blepharoptosis (5.4% (11/203) vs. 0/60). Ptosis was unilateral for all but one subject. Of the 12 eyes affected, eight cases were considered mild, with an average duration of 20 days, and four were considered moderate, with an average duration of 40 days. All cases of ptosis were considered treatment related.

## 5.0 Comments

5.1 This reviewer has checked the sponsor's primary analyses and found that results agree with what the sponsor has presented.

5.2 Worst case analysis: Two of 264 (0.8%) subjects did not receive evaluations at day 30 (key timepoint) and nine subjects (3.4%) had major protocol violations. The reviewer performed worst case analyses for both primary endpoints in which these 11 subjects were treated as non-responders at day 30 if they received BOTOX treatment or considered as responders if they were in the placebo group. Although this is the most conservative analysis, statistically and clinically significant results still hold for both primary endpoints (The investigator's assessment endpoint: 80% response rate in the BOTOX group vs. 3% in the placebo group; The subject's assessment endpoint: 86% response rate in the BOTOX group vs. 3% in the placebo group).

5.3 Placebo effect: In the placebo group, no subject met the responder's criteria for both primary endpoints at day 30 (key timepoint). The only "responder" at day 30 in the placebo group in Tables 1 and 2 is the one who did not complete the study and his score was imputed by the mean of all non-missing data across both treatment groups. It appears that there are almost no placebo effects for both primary endpoints in this study.

5.4 5.4% of subjects treated with BOTOX experienced blepharoptosis. Higher incidences of ptosis could have seriously negative impact on the use of BOTOX for cosmetic purpose. If this problem is likely to be technique-dependent, the sponsor should try their best to minimize the incidence rate.

**PROTOCOL —**

This was a multicenter, double-blind, randomized, placebo-controlled trial with a design that is identical to Protocol 010. Subjects whose glabellar lines were at least moderate severity at maximum frown were eligible for the study. It was planned that 256 subjects would be enrolled and randomly assigned in a ratio of 3:1 to receive a single treatment of intramuscular injections at five sites of either BOTOX (20 units) or placebo. Treatment group assignment was stratified by age group (≤50 years and > 50 years). Post injection evaluations were scheduled on days 7, 30 (key timepoint), 60, 90, and 120.

A total of 273 subjects were enrolled in the study, with 202 subjects randomized to BOTOX and 71 randomized to placebo. All but five subjects, two in the BOTOX group and three in the placebo group, completed the study. Reasons for subjects who withdrew the study prematurely are 1) lost to follow-up (two treated with BOTOX and one with placebo); b) left the study for personal reason (one treated with placebo); c) concurrently participating in another clinical trial (one treated with placebo). However, only one of these five subjects did not receive evaluations at day 30. There are six subjects with major protocol violations: two subjects (one treated with BOTOX and one with placebo) had concomitant facial procedures during the study and four subjects (three treated with BOTOX and one with placebo) were not evaluated by different investigators at days 7 and 30.

The analysis for efficacy was intent-to-treat (ITT), including all randomized subjects. The two co-primary efficacy endpoints were the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines at day 30. The secondary efficacy variable in this study is investigator's assessment of glabellar line severity at rest. The primary procedure of handling missing data for the three efficacy variables are the mean imputation, i.e., at each visit, the mean of all non-missing data across both treatment groups was rounded to an integer value and used to replace these missing values. If a subject discontinued prior to day 30 visit, missing values were replaced up to and including the day 30 visit. All tests were two-sided. BOTOX was claimed more efficacious than placebo only when both co-primary endpoints were statistically significant at the significance level of 0.05 in favor of BOTOX at day 30.

## 1.0 Investigator's Assessment of Glabellar Line Severity at Maximum Frown

One of the two primary endpoints is investigator's assessment of glabellar line severity at maximum frown at day 30. A photoguide, which gave photographic examples of each glabellar line severity, was provided to each study center to assist in grading the severity of glabellar lines. Glabellar line severity scores were coded as 0=none, 1=mild, 2=moderate, and 3=severe.

In the primary analysis, the scores were dichotomized to represent responders (score≤1) and non-responders (score≥2). A Mantel-Haenszel (MH) test stratified by age group (≤50 vs. > 50) was performed to compare the proportions of responders between the two treatment groups. The results are shown in Table 3. The proportion of responders in the BOTOX group was statistically significantly higher than that in the placebo group. At day 30, which was defined as the key timepoint, there was approximately an 73-percentage-point difference in response rates favoring the BOTOX group over the placebo group, exceeding the 30-percentage-point difference required by the first part of the protocol definition of clinically significant results.

**Table 3. Responder Rate for Investigator's Assessment of Glabellar Line Severity at Maximum Frown (% and number of subjects with severity of none or mild)**

| Visit | BOTOX | Placebo | Difference (95% C.I.) | P-value |
|---|---|---|---|---|
| Day 7 | 65.3% (132/202) | 7.0% (5/71) | 58.3 (49.5, 67.2) | < 0.001 |
| Day 30 | 76.7% (155/202) | 4.2% (3/71) | 72.5 (65.0, 80.0) | < 0.001 |
| Day 60 | 65.7% (132/201) | 2.9% (2/70) | 62.8 (55.2, 70.5) | < 0.001 |
| Day 90 | 45.3% (91/201) | 4.4% (3/68) | 40.9 (32.4, 49.3) | < 0.001 |
| Day 120 | 24.4% (49/201) | 2.9% (2/68) | 21.4 (14.3, 28.6) | < 0.001 |

In addition to the primary analysis, the sponsor also conducted a variety of different sensitivity analyses and analyses on subgroup population. The mean baseline (day 0) severity at maximum frown as rated by the investigator was 2.6 in both treatment groups, but the mean rating in the BOTOX group decreased from 1.69 at day 30 to 0.61 at day 120. These decreases were statistically significantly greater than those in the placebo group ($p<0.001$) when the raw severity scores were analyzed using the exact Smirnov test. When the six subjects who had major protocol violations were excluded from the analysis, the results did not differ from those presented for the overall population.

Subgroup analyses of this endpoint by age group, sex, race, investigator, baseline score, and whether subjects had prior BOTOX treatment for facial lines at study entry gave results generally similar to those for the overall population. However, response rates with BOTOX tended to be higher for subjects ≤50, for female, and for subjects whose baseline severity score was moderate.

## 2.0 Subject's Global Assessment of Change in Appearance of Glabellar Line Severity

The other primary efficacy endpoint is subject's global assessment of change in appearance of glabellar line severity at day 30. For this measurement, subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your injection?" The responses were graded a 9-point scale in which +4 =complete improvement, 0 = unchanged, and –4 = very marked worsening.

In the primary analysis, subject's global assessment also was dichotomized to represent responders (scores≥2) and non-responders (scores≤1). A Mantel-Haenszel (MH) test stratified by age group was performed to evaluate the equality of the proportions of responders between the two treatment groups. The results are shown in Table 4. The proportion of subjects reporting moderate or better improvement (score≥2) in the appearance of glabellar lines in the BOTOX group was statistically significantly higher than that in the placebo group. At day 30, which was defined as the key timepoint, there was approximately an 77-percentage-point difference in response rates favoring the BOTOX group over the placebo group, exceeding the 25-percentage-point difference required by the first part of the protocol definition of clinically significant results.

**Table 4. Responder Rate for Subject's Assessment of Change in Appearance of Glabellar Lines (% and number of subjects with at least moderate improvement)**

| Visit | BOTOX | Placebo | Difference (95% C.I.) | P-value |
|---|---|---|---|---|
| Day 7 | 79.2% (160/202) | 12.7% (9/71) | 66.5 (57.0, 76.1) | < 0.001 |
| Day 30 | 88.6% (179/202) | 11.3% (8/71) | 77.4 (68.8, 85.9) | < 0.001 |
| Day 60 | 79.1% (159/201) | 5.7% (4/70) | 73.4 (65.6, 81.2) | < 0.001 |
| Day 90 | 60.2% (121/201) | 4.4% (3/68) | 55.8 (47.4, 64.1) | < 0.001 |
| Day 120 | 33.8% (68/201) | 1.5% (1/68) | 32.4 (25.2, 39.5) | < 0.001 |

In addition to the primary analysis, the sponsor also conducted a variety of different sensitivity analyses and analyses on subgroup population. By day 7 and day 60, the mean rating in the BOTOX group reflected an improvement of more than 2.5 grades, reaching 3 grades at day 30. This improvement dropped to 1.5 grades at day 90 and 1.0 grades at day 120. These results were statistically significantly ($p<0.001$) better at every visit than those in the placebo group which never exceeded 0.4 grades. When the six subjects who had major protocol violations were excluded from the analysis, the results did not differ from those presented for the overall population.

Subgroup analyses of this endpoint by age group, sex, race, investigator, baseline score, and whether subjects had prior BOTOX treatment for facial lines at study entry gave results generally similar to those for the overall population. However, response rates with BOTOX tended to be higher for subjects ≤50, for female, and for subjects whose baseline severity score was moderate.

## 3.0 Investigator's Assessment of Glabellar Line Severity at Rest

Investigator's assessment of glabellar line severity at rest among the potential responders is the secondary efficacy variable in this study. Potential responders were those subjects who had a baseline glabellar line severity score of moderate or severe at rest. This subgroup comprised 93 subjects in BOTOX group and 32 subjects in the placebo group. The proportion of these subjects whose glabellar line severity was rated as none or mild at rest was significantly higher in the BOTOX group than in the placebo group at every follow-up visit except day 120. The response rates in the BOTOX group were 68%, 70%, 70%, 66%, and 53% on days 7, 30, 60, 90, and 120, respectively, compared to 22%, 19%, 22%, 31%, and 34% in the placebo group.

Analyzed across all subjects, the proportion of subjects whose glabellar line severity was rated as none or mild at rest was also significantly higher in the BOTOX group than in the placebo group at every follow-up visit. The response rates in the BOTOX group were 86% and 78% on days 30 and 120, respectively, compared to 62% and 65% in the placebo group.

## 4.0 Safety

Adverse events were reported for 41% of subjects treated with BOTOX and 46% subjects treated with placebo. The most frequently reported adverse event was headache, which was reported for 11% of subjects treated with BOTOX and 20% of subjects treated with placebo. The only adverse event reported for at least 3% of subjects treated with BOTOX was erythema (3%) and the only other adverse event reported for at least 3% of subjects treated with placebo was edema at the injection site (4%). Individual adverse events were reported at similar rates in both treatment groups. Blepharoptosis, which previously has been reported with the use of BOTOX, was reported for two subjects treated with BOTOX. No subjects discontinued the study due to adverse events. Serious adverse events were reported for three subjects treated with BOTOX and one subject with placebo: colon cancer, hepatomegaly, and weight decrease for one subject, and bone disorder, dyspnea, and perforation of the large intestine (placebo) for each of the other three subjects. All these serious events were considered unrelated to study medication.

## 5.0 Comments

5.1 This reviewer has checked the sponsor's primary analyses and found that results agree with what the sponsor has presented.

5.2 Worst case analysis: One of 273 (0.4%) subjects did not receive evaluations at day 30 (key timepoint) and six subjects (2.2%) had major protocol violations. The reviewer performed worst case analyses for both primary endpoints in which these seven subjects were treated as non-responders at day 30 if they received BOTOX treatment or considered as responders if they were in the placebo group. Although this is the most conservative analysis, statistically and clinically significant results still hold for both primary endpoints (The investigator's assessment endpoint: 75% response rate in the BOTOX group vs. 8% in the placebo group; The subject's assessment endpoint: 86% response rate in the BOTOX group vs. 15% in the placebo group).

**PROTOCOL** [redacted]

This was a multicenter, open-label study of repeated treatments with BOTOX in the treatment of glabellar lines. The purpose of this study was to determine if the robust results reported to date are maintained over repeated cycles of treatment, and if the safety profile remains equally benign. Subjects who had completed study [redacted] and whose glabellar lines were at least mild in severity at the time of exit from those studies were eligible to enroll. Two treatments of intramuscular injections of BOTOX were to be administered. The first treatment was to be given on day 0, which was the same day as day 120 (exit visit) of study [redacted]. The second treatment was to be given on day 120 if the subject continued to qualify. Evaluations were scheduled after the first treatment on days 30, 60, 90, and 120, and after the second treatment (administered on day 120) on day 150, 180, 210, and 240.

Five hundred and fourteen subjects, 261 from study [redacted] from study [redacted] were eligible to participate in study [redacted] Three hundred and seventy-three out of the 514 subjects (72%) were enrolled in the study and treated with BOTOX. Of the 373 subjects enrolled in this study, 277 subjects had received BOTOX in the preceding studies and 96 had placebo. Fifty-five subjects who discontinued the open-label study (30 discontinued after the first treatment and 25 discontinued after the second treatment).

The analyses for efficacy and safety included all treated subjects. The primary analysis was the calculation of incidence of adverse events over the entire open-label study period, as well as over each treatment cycle in this study. Efficacy variables were the investigator's rating of glabellar line severity at maximum frown and at rest, and the subject's global assessment of change in appearance of glabellar lines.

## 1.0 Safety Evaluations

Adverse events were reported for 49.1% (183/373) of subjects overall. Adverse events were reported for 49.5% (137/277) of subjects treated in the preceding studies with BOTOX and for 47.9% (46/96) of subjects treated with placebo. The most frequently reported adverse events overall were respiratory infection (39/377, 10.5%), flu syndrome (24/372, 6.4%), and headache (21/373, 5.6%). Blepharoptosis was reported for 11 subjects (2.9%) during the two injection cycles (seven subjects [2.5%] were previously treated with BOTOX and four subjects [4.2%] were previously treated with placebo). There were no apparent differences between adverse events in the type of incidence, severity, or causality of adverse events between the first and second BOTOX treatments. Two subjects discontinued the study for adverse events unrelated to BOTOX, one subject who was diagnosed with breast cancer and one who had an unplanned pregnancy. Six subjects experienced 11 serious adverse events: nausea, vomiting, diarrhea, colitis, bone fracture, fat emboli, knee contracture, breast cancer, herniated disk, urinary incontinence, and lymphadenopathy. All of the serious adverse events were considered unrelated to study medication. No subject died during the study.

## 2.0 Efficacy Evaluations

Thirty days after the first and second treatments the responder rates were at least 86% for both the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines, which were the co-primary efficacy variables in the preceding double-blind studies. The results from analyzing these two endpoints at each visit are presented in Tables 5 and 6, respectively. Other analyses, including the subgroups analyses showed similar efficacy trends to the general population.

**Table 5. Responder Rate for Investigator's Assessment of Glabellar Line Severity at Maximum Frown (% and number of subjects with severity of none or mild)**

| Visit | Treated with BOTOX in Preceding Studies | Treated with Placebo in Preceding Studies | Total |
|---|---|---|---|
| First Treatment Cycle: | (N=277) | (N=96) | (N=373) |
| Day 30 | 85.9% | 85.4% | 85.8% |
| Day 60 | 74.7% | 59.4% | 70.8% |
| Day 90 | 45.5% | 38.5% | 43.7% |
| Day 120 | 23.1% | 18.8% | 22.0% |
| Second Treatment Cycle: | (N=258) | (N=85) | (N=343) |
| Day 150 | 89.1% | 84.7% | 88.0% |
| Day 180 | 97.5% | 72.9% | 77.8% |
| Day 210 | 60.1% | 50.6% | 57.7% |
| Day 240 | 27.5% | 27.1% | 27.4% |

**Table 6. Responder Rate for Subject's Assessment of Change in Appearance of Glabellar Lines (% and number of subjects with at least moderate improvement)**

| Visit | Treated with BOTOX in Preceding Studies | Treated with Placebo in Preceding Studies | Total |
|---|---|---|---|
| First Treatment Cycle: | (N=277) | (N=96) | (N=373) |
| Day 30 | 92.1% | 93.8% | 92.5% |
| Day 60 | 85.9% | 91.7% | 87.4% |
| Day 90 | 68.6% | 66.7% | 68.1% |
| Day 120 | 41.2% | 37.5% | 40.2% |
| Second Treatment Cycle: | (N=258) | (N=85) | (N=343) |
| Day 150 | 90.3% | 96.5% | 91.8% |
| Day 180 | 85.3% | 89.4% | 86.3% |
| Day 210 | 75.6% | 72.9% | 74.9% |
| Day 240 | 54.7% | 54.1% | 54.5% |

## CONCLUSIONS

1. The co-primary efficacy endpoints were met in both pivotal studies ———— Sensitivity and subgroup analyses also support the finding that BOTOX is an effective treatment for reducing the severity of glabellar lines for up to 60 days for most subjects. The efficacy results were consistent when subjects were repeatedly treated in the open-label study ——

2. No serious safety concerns were raised when BOTOX was administered intramuscularly at doses of 20 U, though a higher incidence of blepharoptosis (5.4%) was reported with the use of BOTOX in one of the studies ———

3. The effectiveness of a single dose of 20 U injection could last for up to 60 days for most subjects. At day 90 after the injection, approximately half of the subjects lost their responses. This indicates that about 50% of the subjects in the study population may need to be re-treated at least four times a year in order to maintain their response. However, the benefit/risk ratio in the long-term treatment of glabellar lines with BOTOX in this generally healthy population remains unknown.